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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,324	04/19/2004	Bruce D. Weintraub	TROP-007/03US 304828-2020	1064

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,324	WEINTRAUB ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-142* is/are pending in the application.

4a) Of the above claim(s) *22-30,32-72,74-84 and 86-142* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,21,31,73 and 85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *20-142* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/19/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Invention I in the reply filed on 5/9/2007 is acknowledged.

Applicants election of the species N13B in the reply filed on 5/9/2007 is acknowledged. Applicants have requested (traversed) that the species N13Z also be examined, on the basis that a search for N13B would also reveal art as to the species N13Z. This argument is not strictly correct; different amino acids, with different charges, are being substituted, albeit at the same position. However, the Examiner will agree to examine N13Z as such does not at this time present an undue search burden.

Claims 20, 21, 31, 73 and 85 are under consideration. Claims 22-30, 32-72, 74-84 and 86-142 are withdrawn from prosecution as being drawn to a non-elected invention or species.

Priority

PCT/US98/19772 does not evince the concept of "an electrostatic charge altering mutation in a β hairpin loop structure" of a glycoprotein hormone family member, but rather is drawn to specific mutations in TSH. Further, there is no conception therein of the specifically claimed hCGβ muteins. Accordingly, priority for the claims under consideration is set at 3/19/99.

Information Disclosure Statement

The information disclosure statement submitted 8/19/2004 has been considered.

Claim Interpretation

The claims are drawn to a human glycoprotein family member protein comprising a charge altering mutation in a β hairpin loop structure of an hCG β subunit , said mutation selected from those listed in the claims. There is no generic claim. The listed muteins are not required to have or share any activity or other property associated with the mutation.

It is noted that SEQ ID NO: 3 of the instant specification numbers the residues of human hCGβ differently than is commonly accepted in the art. Specifically, the numbering is off by one amino acid. Thus, the mutation referred to by applicants as "N13B" does not exist in SEQ ID NO: 3; the N residue is found at position 14 of SEQ ID NO: 3. It is noted that in the parent application, this error was not consistent; some residues listed corresponded to SEQ ID NO: 3, others to the art-accepted numbering scheme. Applicants should evaluate *each* listed mutein to determine whether the numbering used in the claim is consistent with SEQ ID NO: 3.

Specification

The disclosure is objected to because of the following informalities: The disclosure should be carefully reviewed for typographical errors. For example, at page 5, line 10, "hCH" should read --hCG--.

Appropriate correction is required.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 20, 21 and 73 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims do not required that the claimed protein be isolated, purified, or otherwise show the hand of the inventor. As species within the metes and bounds of the claims would be reasonably expected to occur in nature, the claims are non-statutory.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20, 21, 31, 73 and 85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because SEQ ID NO: 3 of the instant specification numbers the residues of human hCGβ differently than is commonly accepted in the art. Specifically, the numbering is off by one amino acid. Thus, the mutation referred to by applicants as "N13B" does not exist in SEQ ID NO: 3; the N residue is found at position 14 of SEQ ID NO: 3. However, the art recognizes the intended mutation as being at position 13.

Claim 20 is also indefinite because it is not exactly clear what hormone is being claimed. The preamble states that the claim is to "A human glycoprotein hormone family protein", which would indicate to the person of ordinary skill in the art a set of four hormones, LH, FSH, hCG and TSH. However, the body of the claim states that the claimed hormone must have an electrostatic charge altering mutation in the L1β hairpin loop structure of an hCGβ subunit, at a position selected from the group consisting of positions 1-37 or 589-87 as shown in SEQ ID NO: 3, which is an hCGβ subunit sequence. Because of the use of a broad limitation (human glycoprotein hormone family protein) and a narrow limitation (hCGβ) in the same claim, the claim is indefinite.

Claim 20 is further indefinite as the metes and bounds of the claim cannot be determined because there is no indication of the upper limitation of mutations that may occur, including whether or not said mutations are limited to the recited portions of the molecule, and whether or not any structure and/or function must be maintained. Accordingly, one cannot be informed as to what molecules would or would not fall within the metes and bounds of the claims.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 21, 31, 73 and 85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hCGβ having mutation N13X (X being any amino acid, generically), does not reasonably provide enablement for hCGβ having an unspecified additional number of mutations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is the insertion of a mutation at a certain portion of the hCGβ molecule. The claims are extremely broad: There is no requirement for conservation of any activity. There is no requirement for possession of any activity. There is no upper limit on the number of mutations allowed, either in the specified region of the protein, or elsewhere. All that *is* required is that there be *at least* one electrostatic charge altering mutation in the specified region.

The state of the prior art is that hCGβ is well known in the art. Also, many mutations are known to have been made in hCGβ. However, the state of the prior art is also that it is not predictable what mutations will be tolerated in a protein such as hCGβ, especially considering that there is no upper limit on the number of changes encompassed by the claims. While many

individual substitutions and even some multiple substitutions have been made in the art, it remains a very small number compared to the breadth of the claims.

The relative skill in the art is high with respect to the ability to generate mutated proteins. However, the relative skill in the art is low with respect to being able to predict the effects of said mutations. One illustrative piece of art is Campbell et al., WO91/16922, cited by applicants, wherein specific residues from the beta subunits of each glycoprotein hormone were substituted into at least one of the other members of the family. However, those substitutions evince unpredictability, and do not even begin to address the scope of the pending claims.

There is no specific guidance in the specification as to which species would have what properties. In fact, the specification at page 11 issues an invitation to experiment to determine what properties a molecule might have, stating:

> "The novel mutant CKGFs of the invention alternatively possess: (a) novel properties absent from naturally occurring or wild type CKGFs, or (b) improvements in desirable pharmacological properties that characterize wild type CKGFs. Preferably, when compared with wild type CKGFs, the novel mutant CKGFs disclosed herein have a higher affinity for their cognate receptors. Additionally, the novel mutant CKGFs can be either more active or less active in effecting receptor- mediated signal transduction. In certain embodiments, the novel mutant CKGFs have prolonged half-lives in vivo.
>
> The novel properties possessed by the mutant CKGF proteins arise from the amino acid substitutions, additions, or deletions that alter the electrostatic interactions that occur between the CKGF protein as ligand and its biological receptor. Positively charged residues in the peripheral loops of the CKGF proteins play an important role in receptor interaction. By altering the electrostatic nature of the peripheral loop common to the CKGF superfamily of proteins, mutant CKGF proteins are produced that display increased biological activity as compared to the wild type form of the molecule. Those proteins are one aspect of the present invention."

While hCG is discussed specifically at pages 73-76 of the specification, there is no guidance as to what the expected properties of the claimed muteins would be.

There are no working examples in the specification in which even a single mutein of hCG beta was made.

While the person of ordinary skill in the art would know how to *make* species within the metes and bounds of the claims, the specification has not taught what properties such species would be expected to have. One would know how to use agonists or antagonists, but not species lacking activity. There is insufficient guidance to allow the person of ordinary skill in the art to predict in any manner what characteristics most of the encompassed species would have. The species does not give adequate guidance as to which species would have what function, nor what to do with those that do not have function. Thus, given the breadth of the claims, the lack of working examples, and the unpredictability of the art, it would require undue experimentation to practice the claimed invention in a manner commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20, 73 and 85 are rejected under 35 U.S.C. 102(e) as being anticipated by Campbell et al., WO 91/16922, cited by applicants.

Campbell et al. teach muteins of glycoprotein hormones. A species having the substitution N13E (an acidic residue) is disclosed as species C1; see table III at page 62.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20, 21, 31, 73 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moyle, U.S. Patent No. 7,001,597.

Moyle teaches muteins of hCG, which is produced in the form of a single chain gonadotropin. See Table 1, at column 44, which discloses numerous species with the mutation "N13X" in the hCG beta subunit. At column 45, lines 4-6, "N13X" is defines as "refers to the substitution of glutamine *or other amino acid* (emphasis added) for hCG β subunit residue asparagine 13 and analogs." Moyle teaches that such analogs are useful for various fertility-associated uses, see column 41, which discusses the expected properties of particular analogs.

Thus, Moyle teaches substitutions at N13, wherein the substitution may be any other amino acid. There are twenty naturally occurring, common amino acids. Thus, Moyle may be fairly construed as teaching nineteen possible substitutions at N13. Of those nineteen, two are acidic and three are basic. Thus, 26% of the species suggested by Moyle fall within the metes and bounds of the claims.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute any of the nineteen possible amino acids at the N13 position of hCGβ as taught by Moyle, with the reasonable expectation that they would be useful as taught by Moyle. Moyle discloses the position at which the substitution is to be made, and states that any amino acid may be substituted there. Thus, there is a finite number, 19, of predictable potential muteins disclosed by Moyle. The person of ordinary skill in the art would could have pursued the known potential substitutions, without undue experimentation, and with a reasonable expectation of success. Accordingly, the claimed invention is *prima facie* obvious over Moyle.

The Examiner's position is supported by the recent finding by the Supreme Court in *KSR v. Teleflex, Inc.* (82 USPQ 2d 1385, 4/30/2007), which held that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." (See 82 USPQ2d at 1397.)

Conclusion

No claim is allowed.

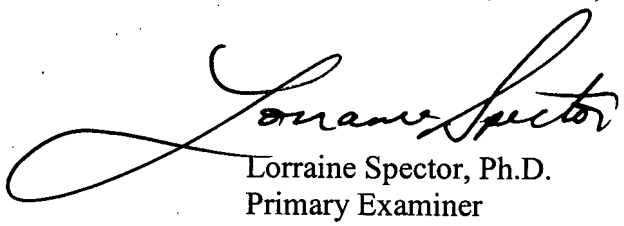
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.
Primary Examiner